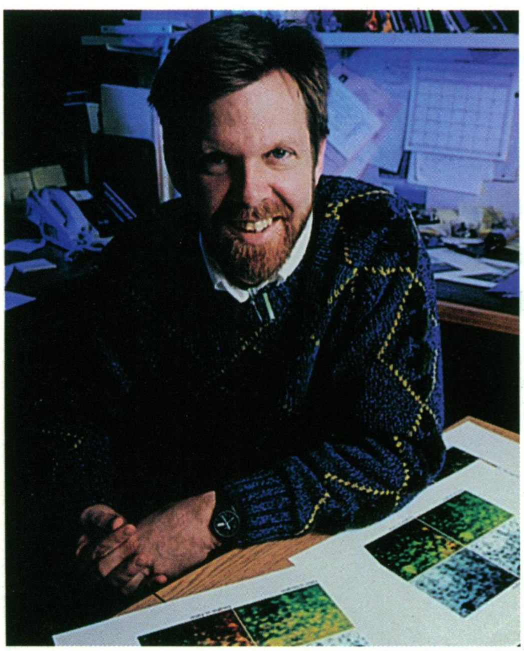
Environment, Genes, and Cancer

In January, comedian George Burns turned 100 years old. In recent appearances in the media, he still seems sharp as a tack, and is still seen smoking his trademark cigars. Others of us, however, were never very funny, and would die of cancer at age 60 if we continuously smoked cigars or cigarettes. Burns presents a common but perplexing paradox: some people are able to tolerate at least moderate exposure to toxins such as cigarette smoke with little adverse affect, while others develop cancer, emphysema, or heart disease.

New studies support the idea that there is an interaction between genes and the environment, and that this interaction may be an important determinant of cancer risk. To understand such risks, it is essential to look at both an individual's genetic makeup and environmental exposures. Such studies require the collaboration of molecular epidemiologists and molecular biologists. At the NIEHS, Jack A. Taylor, a lead clinical investigator in the Epidemiology Branch, and Douglas A. Bell, an investigator with the Genetic Risk Group of the Laboratory of Biochemical Risk Analysis, have worked together and with other scientists to uncover new information in this area.

"Taylor and Bell each have unique talents that complement each other," says Allen Wilcox, chief of the Epidemiology Branch at the NIEHS. "Taylor provides an understanding of population-based research, and Bell is skilled at developing the technical aspects of gene assays. They both share an intuition for connections that might be made between toxic exposures, genetic susceptibility, and cancer risk in human populations."



Steve McCaw, Image Associates

Jack A. Taylor

Genes and environment may interact in different ways to cause disease. In the case of cancer, environmental exposures may cause damage to critical genes involved in cell growth and regulation, thereby initiating cancer. This critical target gene damage is an example of direct gene–environment interaction.

Genes and environment may interact in other ways. The genes we inherit may affect our ability to detoxify a chemical exposure, or to repair DNA damage once it occurs. Thus, variants of certain genes can leave us more susceptible to cancer.

There are a large number of classes of potential susceptibility genes, including allelic variants in DNA repair and fidelity, hormone receptors, cell growth, and carcinogenic metabolizers. These involve both common and rare variants, and present high and low risks of disease. Rare genetic variants, such as *BRCA1* (implicated in some breast and ovarian cancers), confer a very high risk of a particular cancer, and may occur in familial clusters. Other gene variants produce much lower elevations in cancer risk, but occur at much higher frequencies in the population. Such genes may be detected in population-based, case–control studies. At low or moderate exposure to carcinogens, individuals possessing these variants show increased risk.

The growing knowledge in this field presents significant opportunities and challenges to individuals concerned with safeguarding their health, and to policy makers and employers faced with evaluating risks in the environment as well as the workplace, and determining a course of action that protects human health.

Epidemiological Studies

Epidemiological research on gene–environment interactions began at the NIEHS with Taylor's arrival in the mid-1980s. Taylor took a particular interest in the interaction between genes, the environment, and bladder and lung cancer—the two types of cancer most closely associated with environmental exposure.

"Animal data showed that exposure of mice and rats to certain chemicals could cause specific mutations in proto-oncogenes, turning them into oncogenes," Taylor says. "I wanted to see if this occurred in humans. So in 1986, I began collecting tumors from people with high occupational exposure to see what patterns of mutation were caused in critical target genes."

Over the next decade, Taylor directed a variety of studies looking at genetic defects in tumors from people with different exposures. In studies of lung cancer, Taylor examined populations exposed to uranium, nickel, asbestos, vinyl chloride, and cigarette smoke. Taylor's bladder cancer studies dealt with workers exposed to highly carcinogenic arylamine, patients treated with the chemotherapeutic agent cyclophosphamide, and smokers and nonsmokers.

The laboratory phases of these studies, carried out in collaboration with NIEHS scientist Teddy Devereaux and molecular biologists elsewhere, initially focused on the mutational activation of *ras* family oncogenes and deactivation of the tumor suppresser gene *p53*, both of which appear to be frequent early events in the genesis of lung and bladder cancers. The studies on lung tumors in uranium miners showed that 32% of large and squamous cell cancers from miners had an identical mutation in *p53*, while this mutation was very rare in tumors from smokers. This rather surprising result provides support for the idea that different carcinogens may cause different mutational "fingerprints," although Taylor points out in a recent study that such mutations do not occur in all types of lung cancers in uranium miners.

Molecular epidemiology studies help identify the pathways by which environmental agents initiate tumors. At the same time, the defects present in tumors may help to reveal what types of environmental exposures are causing different cancers.

Genetic Susceptibility Studies

While conducting studies in critical target genes, Taylor began another study designed to look at genetic susceptibility and gene–environment interaction in bladder cancer. In collaboration with urologists at Duke University and the University of North Carolina at Chapel Hill, he collected data from over 200 cases and 200 control subjects over a four-year period in the late 1980s. Although methods for genotyping large populations were not well developed at the time and few genes had been cloned, Taylor reasoned that by the time his study was out of the field, such techniques would be available.

"We knew that both environmental exposures and genetics were important to bladder cancer risk, and I wanted to design a study that looked at genetic susceptibility and environmental exposures simultaneously," says Taylor. "That opportunity came along when Doug Bell arrived."

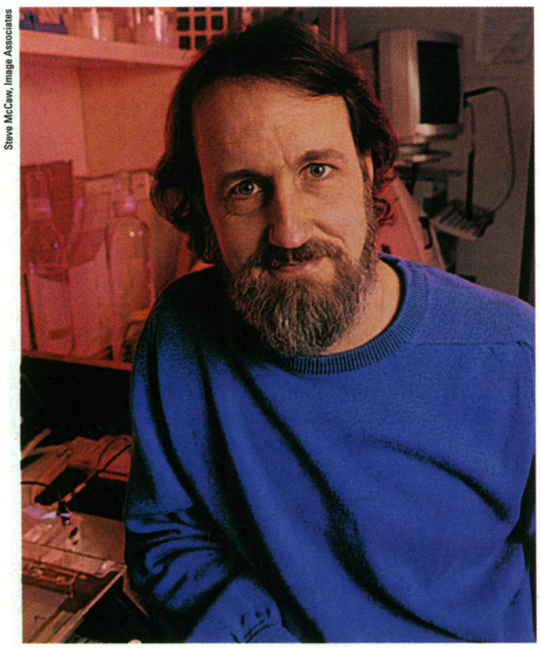
In 1990, Bell joined the NIEHS staff. Bell knew how to rapidly clone and identify mutations in metabolism genes using a molecular genetic technique known as polymerase chain reaction. Bell and Taylor formed a collaboration to explore the potential association between carcinogen metabolism gene polymorphisms and risk in the samples Taylor had previously collected.

Two classes of enzymes, the *N*-acetyltransferases (*NAT1* and *NAT2*) and glutathione-S-transferases (*GSTM1* and *GSTT1*), play important roles in the metabolism of carcinogens such as polycyclic aromatic hydrocarbons and aromatic amines—carcinogens found in tobacco smoke, air pollution, occupational exposures, and dietary sources. These enzymes are expressed only in certain tissues in the body. For example, *NAT2* is present primarily in the liver, while *NAT1* is more highly expressed in the bladder and colon. Scientists have theorized that polymorphisms in such genes affect the efficiency of activation or detoxification of environmental carcinogens, and may play a role in the development of cancer in those organs.

In their first results, Bell and Taylor showed that people who inherited two defective copies of *GSTM1* had a twofold increased risk of bladder cancer compared to people who inherited a functional copy of the gene. The presence or absence of the gene only affected risk in people who were smokers.

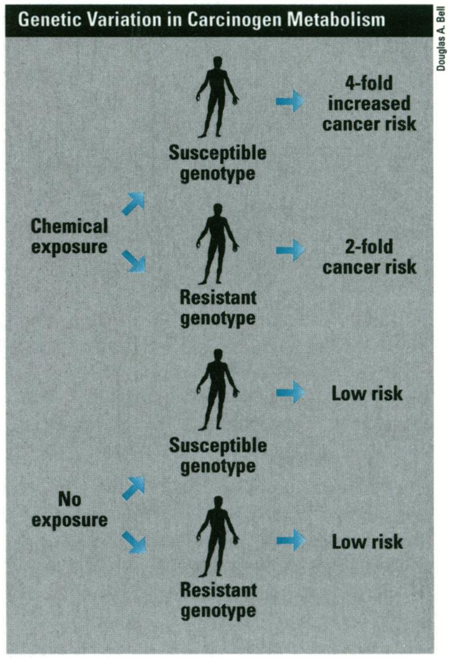
Previous studies had suggested that *NAT1* might play an important role in the metabolism of aromatic amines, carcinogens found in cigarette smoke and well-cooked meats. Variations in *NAT1* activity among human populations might affect the risk of DNA damage in tissues and subsequent risk of bladder and colon cancer. Working with Fred Kadlubar, a researcher with the National Center for Toxicological Research, Bell found twofold higher *NAT1* enzyme activity in samples from individuals who inherited a variant polyadenylation signal known as the *NAT1**10 allele. This was the first observation to relate a genetic polymorphism in *NAT1* to a high-activity *NAT1* phenotype in humans.

Next, Bell and Kadlubar sought to determine how these polymorphisms modulate DNA adduct formation in the human bladder. Adducts mark the binding of a chemical to DNA. They can cause miscoding of DNA during replication, which can subsequently lead to mutations and cancer. This study compared levels of aromatic amine–DNA adducts among individuals with different *NAT1* and *NAT2* genotypes. Individuals with the rapid *NAT1* genotype (*NAT1**10 allele) were found to have twice the aromatic amine–DNA adducts compared to those with the normal activity *NAT1* genotype. In addition, individuals with the combined high-risk genotypes for both *NAT1* and *NAT2* had the highest level of bladder adducts.



Douglas A. Bell

With this knowledge in hand, Bell teamed up with Richard Strange, a researcher from Keele University in North Staffordshire, England, to analyze a case–control study of 202 colorectal patients to determine if the *NAT1**10 allele increases the risk of colorectal cancer. The study found a 1.9-fold increased risk of cancer associated with the *NAT1**10 allele. In contrast, rapid acetylation genotypes of *NAT2* were found not to significantly increase cancer risk in this group. However, the study found that the risk associated with *NAT1**10 was most apparent among those with high risk *NAT2* genotypes, suggesting a possible gene–gene interaction between *NAT1* and *NAT2*.



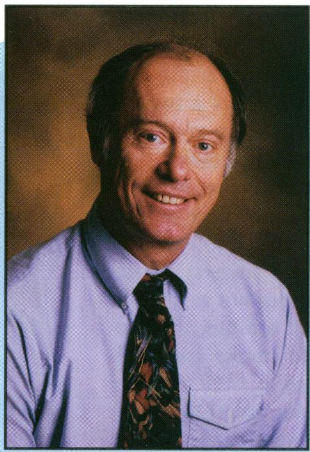
Bell and Taylor have recently collaborated on a similar study to determine if *NAT1* and *NAT2* play a role in the development of bladder cancers associated with aromatic amine exposure. Results of this study point to a positive association between the *NAT1*10* allele and increased risk of bladder cancer.

In collaboration with NIEHS epidemiologist Dale Sandler, Bell and Taylor have also studied the impact of *GSTM1* and *GSTT1* polymorphisms on the risk of developing myelodysplastic syndromes (MDS), anomalies of the spinal cord. Hongwei Chen, a researcher in Bell's lab, has found that individuals with two defective copies of the *GSTT1* gene are at a fourfold risk of developing MDS.

The work of Taylor and Bell provides further evidence that individuals vary in their response to exposure to environmental chemicals. This knowledge should help improve the accuracy of risk assessment and allow preventative methods to be prescribed for targeted individuals. Scientists predict that within the next ten years it will be possible to develop cancer-risk profiles for individuals. Such profiles can help steer individuals away from certain environmental agents, or may direct screening of those individuals known to be at greater risk.

John Manuel

Lucier Named Director of ETP



Steve McCaw, Image Associates

In December, NIEHS Director Kenneth Olden announced the appointment of George Lucier as director of the institute's Environmental Toxicology Program (ETP). In making the announcement Olden said, "[Lucier's] unique breadth of abilities—as a scientist, administrator, and editor—along with his highly focused ability to get tasks accomplished make him an excellent choice for this key role in ensuring the health of the American people."

Lucier, chief of the NIEHS Laboratory of Biochemical Risk Analysis and co-editor-in-chief of *Environmental Health Perspectives*, became acting director of the ETP in 1993. The ETP is the NIEHS component of the National Toxicology Program (NTP) that coordinates toxicology research and testing within the Department of Health and Human Services. The NTP provides toxicological evaluations on chemicals of public health interest; develops and validates improved (more sensitive and specific) methods of performing such evaluations; generates scientific information to strengthen the basis of public health and industrial safety and regulatory decisions; and communicates NTP findings to stakeholders.

One of the major new initiatives of the NTP is to develop strategies for incorporating all relevant data including mechanistic information, into toxicological evaluations. The NIEHS funds approximately one-third of toxicology studies worldwide.

Upon assuming the directorship, Lucier said he plans to focus his energies on ensuring that the program's toxicological testing provides the necessary data to strengthen the scientific foundation of risk assessments and to reduce uncertainties associated with current risk assessment practices. "This is best accomplished when scientific information is available from a number of sources," said Lucier, "including toxicology, mechanistic data, human studies, and mathematical models." Lucier said the program will work with regulatory agencies to determine the information needed to make appropriate risk assessment decisions.

In addition to continuing to integrate the ETP's activities with other NIEHS research efforts, Lucier plans to direct efforts to creating partnerships with industry and regulatory agencies to develop and validate faster and less expensive testing methods that will enable more chemicals to be tested. "Partnerships will lessen the time needed to develop databases of sufficient size to validate new assays," said Lucier. "The first step in this direction occurred February 9, in an NTP/industry meeting on the validation of transgenic models in toxicity testing held at the NIEHS."

Lucier joined the NIEHS in 1970 after obtaining a BA from Clark University and a PhD in agriculture from the University of Maryland. He also serves as an adjunct professor at the University of North Carolina at Chapel Hill on the faculties of biochemistry, nutrition, and toxicology.